A DOUBLE-BLIND TRIAL OF DUROPHET-M IN THE TREATMENT OF OBESITY IN GENERAL PRACTICE

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A large number of the conditions which general practitioners are called upon to treat are the outcome of, or exacerbated by, obesity. In fact, obesity is *the* nutritional problem of our society and it is perhaps a reflection of the increased intake of carbohydrates in the western world (Yudkin, 1963).

It is generally accepted that obesity is the result of more calories being ingested than are expended—a state of affairs leading to the deposition of adipose tissue. Such excess weight can only be lost if the reaction is reversed; when the calorie expenditure exceeds the intake, the patient loses weight. While the expenditure side of the equation is important (Kennedy, 1961), it is easier to reduce intake than increase expenditure. Thus the sheet-anchor of most weight-reducing programmes is a low-calorie diet. However, although it is relatively easy for the doctor to diagnose obesity and prescribe an adequate diet, it is extremely difficult for the patient to adhere to the diet, and in general the results of the dietary treatment of obesity are poor (Stunkard and McLaren, 1959). Therefore any measure which will help patients keep to a diet, and relieve the general practitioner of the need to make repeated exhortations, would be welcome.

It was with this consideration in mind that we undertook a double-blind clinical trial of a new anorectic preparation, durophet-M, which is a mixture of laevo- and dextro-amphetamine plus methaqualone in a sustained release form. Durophet alone has been shown to be effective in helping patients reduce their calorie intake (Smith, 1962), but as yet there have been no controlled clinical trials in this country of durophet-M. A preparation which contains both the anorectic agents plus a tranquillizer should theoretically lessen the psychological difficulties of dietary restriction.

Material and method

Subjects. Eighty-eight patients in one general practice, known to be overweight, were asked if they would like to attend a special clinic outside surgery hours where they would be given help to reduce weight (Lascelles

and Silverstone, 1964). Seventy-two patients accepted the offer and were randomly allocated to one of eight groups (see below). Each patient was given a specific appointment on the clinic evening and was seen once a fortnight for 16 weeks. One of us (B.D.L.) at each attendance recorded their weight, blood pressure, and asked about their general health plus possible side-effects. The other (J.T.S.) rated hunger, anxiety, depression and insomnia occurring in the previous fortnight (Silverstone and Lascelles, 1964). These findings will be reported in detail elsewhere. If a patient failed to attend on any one occasion he was reminded of the date of the next clinic.

Diet. Each patient was given a low carbohydrate diet, previously shown to be as effective as a 1,000 calorie diet, yet much easier to follow (Silverstone and Lockhead, 1963).

Drug. The anorectic agent used was durophet-M 12.5 mg. which is a combination of amphetamine (1:3 ratio of laevo- and dextro-amphetamine) together with methaqualone, a quinazalone compound possessing tranquillizing properties (Gujral *et al.*, 1955). Each capsule contained amphetamine B.P. 6.25 mg., and dexamphetamine 6.25 mg., thus providing a ratio of laevo- and dextro-amphetamine of 1:3. This has been shown to be the optimum ratio by Freed and Mizel (1952). The dosage of methaqualone was 40.0 mg.

All the medicaments were present as ion-exchange resin complexes formed by combination with a sulphonic acid cation exchange resin, from which they are released at a uniform rate over 10–14 hours. The rate of release is independent of intestinal activity or pH (Sensenbach and Hays, 1960). Each patient took one capsule of drug or an identical placebo capsule each morning. Which capsule they took during any one month was determined by the group they were in. The nature of the capsules was not known by either doctor or by the patients. The drug regimes for each group are given in table I. Nine patients were allocated to each group.

Results

Of the 72 patients who were originally in the trial, 60 patients (83 per cent) attended for the 16 week period of the trial. Of the 12 defaulters, it is interesting to note that three stopped coming after losing between 14 and 18 lbs: two came for only the first two sessions: one moved out of the district: one was discovered to have carcinoma of the bladder: one complained the capsules caused palpitations. The details of the 60 patients completing the trial are given in table I.

Weight loss. For each of the four months of the trial the mean weight lost by all those who received durophet-M during the month was compared with the mean weight lost by those who received placebo. The results are plotted graphically in figure 1. From this figure it can be seen that in the first month those receiving placebo lost almost as much weight as those receiving durophet-M. However, in each of the subsequent three months the patients on durophet-M for the month lost substantially more weight than those on placebo.

If, as it appears, durophet-M is more effective than a placebo in assisting patients to keep to their diet and thus lose weight during the latter three

TABLE I
D=durophet-M P=placebo

Group and drug regime	No.	Sex	Age	Height ft in.	Initial weight lbs	Wt. lost per month 1	2	3	4	Total weight lost lbs	Side-effects
1.	1	F	27	5– 2	184	16	6	3	8	33	
	2	F	31	5– 2	185	0	5	1	3	9	
	3	F	42	5– 6	169	11	9	4	5	29	
DDDD	4	M	35	5– 5	163	4	6	3	4	17	
	5	M	53	5– 8	182	—3	0	8	5	10	
	6	F	50	5– 1	154	10	8	2	3	23	
	7	F	61	5– 0	140	5	5	2	1	13	Blurred vision 1 week
	8	M	51	5– 6	170	12.5	7.5	2	5	27	
2.	9	F	57	5– 4	176	7	10	—2	4	19	
	10	M	63	5– 3	186	6	8	4	—2	16	
	11	M	34	5– 9	200	10	2	0	—1	11	
	12	M	56	5– 5	191	13	6.5	0	7.5	27	
PDDP	13	F	56	4–11	130	4	4	4	1	13	
	14	F	40	5– 2	172	3	8	0	1	12	Anxiety
	15	F	44	5– 1	186	6	7	—1	5	17	
	16	F	49	5– 4	177	2.5	3	2	—2.5	5	
	17	M	70	5– 3	168	6	8	1	0	15	
3.	18	F	41	5– 3	142	4	4	—4	1	5	
	19	F	47	5– 4	186	11	8	3	6	28	
	20	F	27	5– 5	188	7	8	—1	2	16	Headache and nausea
PDPD	21	F	44	5– 2	170	7	3	1	2	13	Palpitations
	22	F	41	5– 5	177	6.5	2.5	1	5	15	
	23	F	54	5– 3	190	4.5	9.5	3	7	24	
	24	F	65	4–11	156	1	0	0	—1	0	
	25	F	48	5– 5	177	6	5	5	—1	15	
	26	F	36	5– 4	249	2.5	12.5	0	—4	11	
4.	27	M	66	5– 8	224	7	3	3	6	19	
	28	F	12	4– 7	126	7	3	4	0	14	
	29	F	55	5– 1	154	7	5	3	5	20	
PPDD	30	F	45	5– 4	198	7.5	2	—1.5	4	12	
	31	F	68	4– 9	191	5	0	7	8	20	
	32	F	55	5– 2	191	9	3	4	3	19	
	33	M	35	5–10	282	9.5	5.5	1	10	26	
5.	34	F	20	5– 4	154	7	3.5	0	—4.5	6	
	35	F	53	4– 7	185	2	6	1.5	—2.5	7	
DDPP	36	F	34	5– 0	142	2	4.5	—1	2.5	8	
	37	F	51	5– 5	215	8.5	1.5	—1	0	9	

TABLE I (*continued*)

Group and drug regime	No.	Sex	Age	Height ft. in.	Initial weight lbs	Wt. lost per month 1	2	3	4	Total weight lost lbs	Side-efiects
6.	38	F	31	5– 3	167	11	0	1	1	13	
	39	F	37	5– 2	148	9	10	3	3	25	
	40	F	55	5– 2	144	6	2	2	4	14	
DPDP	41	F	59	5– 0	156	3.5	4	2.5	2	12	
	42	M	70	5– 6	174	4.5	0.5	3	4	12	
	43	F	59	5– 0	223	7	—1.5	4	—3.5	6	
	44	F	72	5– 3	173	12	3	4	—4	15	Giddiness for
	45	F	65	5– 2	157	2.5	1.5	2	6.5	12	1 week
7.	46	F	48	5– 4	200	10	9	4	3	26	
	47	F	73	5– 0	167	1	1	—2	0	0	
	48	M	58	5–10	196	1	6	1	0	8	
DPPD	49	M	56	5– 7	244	10	6	0	2	18	
	50	F	24	5– 5	210	13	—4	—2	5	12	
	51	M	53	5– 7	182	8	5	—2.5	5.5	16	
	52	F	39	5– 2	145	4.5	2.5	4	—2	9	
	53	F	65	5– 2	205	7.5	3	1	5.5	17	
8.	54	F	62	5– 7	174	9	—1	5	3	16	
	55	F	55	5– 2	158	6	1	—3	—1	3	
	56	F	54	5– 0	172	7	2.5	5	3.5	18	
PPPP	57	F	16	5– 4	168	14	2	3.5	1.5	21	
	58	M	65	6– 1	195	0	—2	0	—2	—4	
	59	M	50	6– 0	212	9	5	2	1	17	
	60	F	50	5– 6	196	4	4	0	3	11	

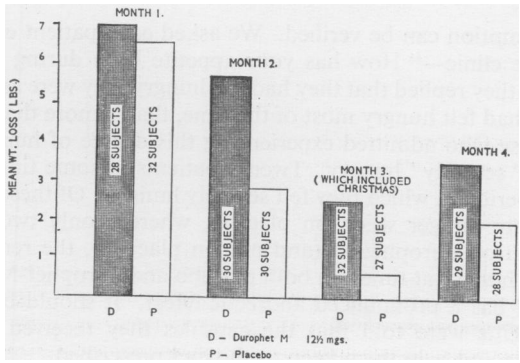

Figure 1.

months of the trial, then it would be expected that those who received durophet-M for all three of these months (group 1) should lose more weight than those receiving it for two of these months (groups 2, 3 and 4). Similarly, those receiving durophet-M for two of these three months should lose more weight than those receiving it for only one month (groups 5, 6 and 7), and again those receiving it for one month should lose more than those who received only placebo for the three months (group 8).

The actual results confirm this expectation. If the weight loss in the last three months of the trial is correlated with the *number* of months on the active preparation (i.e. 0, 1, 2 or 3) a highly significant regression is obtained ($P < 0.01$). This is shown in table II where the mean weight loss varied from 11.7 lbs in those receiving no active drug to 20.0 lbs in those receiving active drug during each of the latter three months.

TABLE II

Groups	*Tablets received in last 3 months of trial*			*No. patients*	*Mean weight lost*	*S.E.*
1	*D*	*D*	*D*	8	20.0	±2.7
2	*D*	*D*	P			
3	*D*	P	*D*	25	15.6	±1.4
4	P	*D*	*D*			
5	*D*	P	P			
6	P	*D*	P	20	12.5	±1.4
7	P	P	*D*			
8	P	P	P	7	11.7	±3.3

D=durophet-M P=placebo

Hunger. These results demonstrate the effectiveness of durophet-M in assisting patients to lose weight. We assumed that the drug acted by decreasing appetite and therefore enabled patients to adhere more strictly to their diet.

This assumption can be verified. We asked each patient every time he attended the clinic—" How has your appetite been during the last two weeks? " If they replied that they had felt hungry they were asked whether or not they had felt hungry most of the time, that is more than four hours a day. Those who admitted experiencing this degree of hunger we refer to as being ' severely ' hungry. Twenty patients at some time during the trial had a period in which they felt severely hungry. Of these 20 patients, 14 had severe hunger when on placebo, whereas only two had severe hunger when on durophet-M (and not on placebo), the remaining four felt severely hungry at times on both placebo and durophet-M. Therefore durophet-M has a pronounced anorectic effect. It should be noted that all the patients were told that the capsules they received would curb their appetite and help them keep to the diet prescribed.

Side-effects. Only six patients complained of side-effects while on the active drug and none while on placebo (table I). Two patients experienced

palpitations; one had blurred vision for a week; one was anxious and one had headache and nausea; the sixth complained of giddiness. None of the symptoms was particularly severe, and in no case was it necessary to stop treatment because of them. However, one of the patients with palpitations failed to complete the trial.

Conclusions

In the present trial it has been shown that the new preparation durophet-M is an effective agent in the treatment of obesity in general practice. Although during the first month of the trial durophet-M was no better than a placebo, in the subsequent three months the total weight lost was significantly correlated with the number of months the patients received durophet-M. In keeping with this was the finding that far fewer patients felt severely hungry when on durophet-M than when on placebo. We thus confirmed the findings of Harris *et al.* (1947), who showed that amphetamine induced weight loss mainly by curbing appetite.

The fact that the total weight lost depended, during the last three months, on the number of months which durophet-M was given suggests that tolerance to this drug was minimal during the period of study.

The side-effects were few and did not warrant cessation of treatment. No cases of dependence on the drug appeared.

On the basis of our results we make the following recommendations for the treatment of obesity in general practice. A suitable diet which ensures a calorie intake of about 1,000 calories and which is easy to follow should be given and explained to each patient. Emphasis should be laid on items permitted as well as those forbidden. Frequent, regular attendances are necessary to enable the patient to ask the practitioner any question he might have about the diet and also to enable the practitioner to ensure that the patient is maintaining a satisfactory weight loss. In order to curb the appetite and thus assist patients in keeping to their diet we are of the opinion that durophet-M 1 capsule daily can be given to advantage for a period of four months. Any longer period of medication might lead to dependence on or addiction to the amphetamine content and therefore should be undertaken only with extreme caution. After sufficient interval, further courses of anorectic agents will be needed with some patients.

The fact that 83 per cent of the patients completed the trial and only one of those failed to lose weight is evidence that successful treatment of obesity is possible for the large majority of patients in general practice. Our experience encourages us to suggest that such treatment is most successfully undertaken when a particular time is set aside each week or fortnight for the management of these patients.

Summary

1. A double-blind trial of a new anorectic agent, durophet-M, in general practice is described.
2. 60 (83 per cent) of the 72 commencing completed the 16-week trial.
3. Durophet-M was found to be more effective than a placebo in the last three months of the trial.
4. Twenty patients felt severely hungry at some time during the trial, of

these 14 felt severely hungry when on placebo only, whereas two felt severely hungry only when on durophet-M.

5. The significance of these findings is discussed and recommendations made on the treatment of obesity in general practice.

Acknowledgement

We should like to express our gratitude to Dr P. W. S. Gray of Riker Laboratories for his assistance in organizing the trial and for supplying durophet-M and placebo capsules, and to Mr M. P. Curwen for kindly advising on the statistics.

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A COMPARISON OF THE THERAPEUTIC EFFECT OF THE INTRA-ARTICULAR INJECTION OF TWO LONG-ACTING STEROID COMPOUNDS ON DEGENERATIVE JOINTS

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IN A PREVIOUS PAPER the writer attempted to compare the value of prednisone trimethylacetate (ultracortenol, Ciba) and hydrocortisone in degenerative joint disease. The former was shown to be more effective than the latter.

The present paper is the result of a clinical trial designed to compare the effectiveness of prednisone trimethylacetate (ultracortenol, Ciba) and methyl prednisolone acetate (depomedrone, Upjohn).

The work was done on patients attending the clinic for arthritic patients at Northwood, Pinner and District Hospital. All patients are referred to this clinic by the consultant orthopaedic surgeon or the consultant in